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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
SHEIKH, HUMERA N	

ART UNIT	PAPER NUMBER
1615	

DATE MAILED: 10/03/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/824,391	PAIRET ET AL.	
	Examiner	Art Unit	
	Humera N. Sheikh	1615	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *14 April 2004*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-9,17-19,24,25,54-56 and 59-65* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-9,17-19,24,25,54-56 and 59-65* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☒ Certified copies of the priority documents have been received in Application No. 10/007,182.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *04/14/04*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Status of the Application

Receipt of the Preliminary Amendment and the Information Disclosure Statement (IDS), both filed 04/14/04 is acknowledged.

Claims 1-9, 17-19, 24, 25, 54-56 and 59-65 are pending. Claims 1-9, 17-19, 24-25 and 54-55 have been amended. New claims 59-65 have been added. Claims 10-16, 20-23, 26-53 and 57-58 have been cancelled. Claims 1-9, 17-19, 24, 25, 54-56 and 59-65 are rejected.

Claim Objections

Claim 1 is objected to because of the following informalities:

Claim 1 recites '...selected from glucose, arabinose, etc.'. The claim should instead be recited as '*selected from the group consisting of*' to be in proper Markush format. Appropriate correction is required.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

Claims 1-9, 17-19, 24, 25, 54-56 and 59-60 are rejected under 35 U.S.C. 103(a) as being unpatentable over Sarlikiotis *et al.* (US Pat. No. 6,284,287) in view of Garvey *et al.* (US Pat. No. 5,824,669).

The instant invention is drawn to an inhalable powder pharmaceutical composition comprising: (a) a tiotropium salt; (b) an antihistamine; and (c) a pharmaceutically acceptable excipient selected from glucose, arabinose, lactose, saccharose or maltose, the tiotropium salt and the antihistamine optionally in the form of their enantiomers, mixtures of their enantiomers, their racemates, their solvates or their hydrates.

Sarlikiotis *et al.* ('287) teach a pharmaceutical formulation for administration by inhalation, comprising a mixture of active compounds that include anticholinergics, such as atropine, atropine methonitrate, ipratropium bromide, oxitropium bromide and trospium chloride and antihistaminics, such as azelastine, flezelastine and methapyrilene (see abstract and col. 3, line 24 through col. 4, line 4). The active compounds can be employed as free bases, acids or as pharmaceutically tolerable salts. Counterions that can be employed are, for example, amines, bromide, chloride, iodide, carbonate, etc. (col. 3, lines 55-65).

The formulation, which can consist of a mixture of several finely ground active compounds also contains excipients, which have a mean particle size of 200-1000 microns. Suitable excipients are for example, inorganic and organic salts, monosaccharides, such as *glucose* and its derivatives, disaccharides, such as *lactose, maltose and derivatives*, polysaccharides, such as starch and its derivatives and oligosaccharides, such as cyclodextrins. Mixtures of the auxiliaries can also be employed. The ratio of the active compound to the excipient material depends on the substances employed (see col. 3, line 65 through col. 4, line 25).

Sarlikiotis teaches anticholinergics, such as ipratropium bromide. Sarlikiotis does not teach a tiotropium salt and a kit comprising dosage containers.

Garvey *et al.* ('669) teach pharmaceutical compositions for the treatment of respiratory disorders comprising therapeutically effective amounts of anticholinergic agents, such as atropine, ipratropium, flutropium, *tiotropium* and rispenzepine (see col. 2, line 12 through col. 6, line 55). According to Garvey *et al.* anticholinergic agents such as tiotropium, ipratropium, etc. are known to be useful in treating inhalational respiratory diseases, such as asthma (col. 2, lines 12-19). Garvey *et al.* also teach a pharmaceutical pack or kit comprising one or more containers filled with one or more of the ingredients of the pharmaceutical compositions of the invention (col. 29, lines 50-58).

Therefore, it would have been obvious to one of ordinary skill in the art at the time the invention was made to incorporate the tiotropium salts and kit taught by Garvey *et al.* within the

composition of Sarlikiotis *et al.* because Garvey *et al.* teach that anticholinergic agents, such as tiotropium, ipratropium, etc. are useful and effective in the treatment of respiratory diseases. The expected result would be an improved tiotropium/antihistamine composition for treating respiratory disorders.

Claims 1-9, 17-19, 24, 25, 54-56 and 59-60 are rejected under 35 U.S.C. 103(a) as being unpatentable over Garvey *et al.* (US Pat. No. 5,824,669) in view of Naclerio (Clinical and Experimental Allergy-1998).

The instant invention is drawn to an inhalable powder pharmaceutical composition comprising: (a) a tiotropium salt; (b) an antihistamine; and (c) a pharmaceutically acceptable excipient selected from glucose, arabinose, lactose, saccharose or maltose, the tiotropium salt and the antihistamine optionally in the form of their enantiomers, mixtures of their enantiomers, their racemates, their solvates or their hydrates.

Garvey *et al.* ('669) teach pharmaceutical compositions for the treatment of respiratory disorders comprising therapeutically effective amounts of anticholinergic agents, such as atropine, ipratropium, flutropium, *tiotropium* and rispenzepine, wherein the compositions contain conventional excipients, such as *lactose* and amylose and are preferably administered by inhalation (oral and/or nasal) (see col. 2, line 12 through col. 6, line 55); (col. 28, lines 3-24).

Garvey *et al.* also teach a pharmaceutical pack or kit comprising one or more containers filled with one or more of the ingredients of the pharmaceutical compositions of the invention (col. 29, lines 50-58).

Garvey *et al.* are deficient in the sense that they do not teach the combined use of an anticholinergic with an antihistamine.

Naclerio teaches a study based on allergic rhinitis wherein the combination of an anticholinergic, such as ipratropium bromide combined with an antihistamine, can provide additional benefits, as compared to using the anticholinergic or anthistamine alone. The study suggests a synergistic effect can be obtained for the treatment of allergic rhinitis when both active ingredients are administered simultaneously (see pgs. 54-59).

Therefore, it would have been obvious to one of ordinary skill in the art at the time the invention was made and one would be motivated to use the teachings of Naclerio, who teaches beneficial results of the combined use of an anticholinergic and antihistamine, within the formulation of Garvey *et al.* because Naclerio teaches that a synergistic effect is obtained with the combined use of an anticholinergic and an antihistamine. The expected result would be an effective pharmaceutical formulation for respiratory-related diseases and disorders.

Claims 1-9, 17-19, 24, 25, 54-56 and 59-60 are rejected under 35 U.S.C. 103(a) as being unpatentable over Naclerio (Clinical and Experimental Allergy-1998) in view of Garvey *et al.* (US Pat. No. 5,824,669) and further in view of Sarlikiotis *et al.* (US Pat. No. 6,284,287)

The instant invention is drawn to an inhalable powder pharmaceutical composition comprising: (a) a tiotropium salt; (b) an antihistamine; and (c) a pharmaceutically acceptable

excipient selected from glucose, arabinose, lactose, saccharose or maltose, the tiotropium salt and the antihistamine optionally in the form of their enantiomers, mixtures of their enantiomers, their racemates, their solvates or their hydrates.

Naclerio teaches a study based on allergic rhinitis wherein the combination of an anticholinergic, ipratropium bromide combined with an antihistamine, can provide additional benefits, as compared to using the anticholinergic or anthistamine alone. The study suggests a synergistic effect can be obtained for the treatment of allergic rhinitis when both active ingredients are administered simultaneously (see pgs. 54-59).

Naclerio teaches the use of ipratropium bromide with an antihistamine and is lacking in the sense that he does not teach tiotropium salt.

Garvey *et al.* ('669) teach pharmaceutical compositions for the treatment of respiratory disorders comprising therapeutically effective amounts of anticholinergic agents, such as atropine, ipratropium, flutropium, *tiotropium* and rispenzepine, wherein the compositions contain conventional excipients, such as *lactose* and amylose and are preferably administered by inhalation (oral and/or nasal) (see col. 2, line 12 through col. 6, line 55); (col. 28, lines 3-24).

Therefore, it would have been obvious to one of ordinary skill in the art at the time the invention was made to incorporate the tiotropium salts taught by Garvey *et al.* within the teachings of Naclerio because Garvey *et al.* teach that anticholinergic agents, such as tiotropium, ipratropium, etc. are useful and effective in the treatment of respiratory diseases. The expected result would be an effective and enhanced pharmaceutical formulation for the treatment of respiratory disorders, as similarly desired by the applicant.

Naclerio, as discussed above, teaches the use of ipratropium bromide with an antihistamine and is lacking in that he does not teach the instant excipients.

Sarlikiotis *et al.* ('287) teach a pharmaceutical formulation for administration by inhalation, comprising anticholinergics, antihistaminics and excipients (see abstract and col. 3, line 24 through col. 4, line 4). Suitable excipients taught include, for example, glucose and its derivatives, disaccharides, such as lactose, maltose and derivatives, polysaccharides, such as starch and its derivatives and oligosaccharides, such as cyclodextrins (col. 3, line 65 through col. 4, line 25). According to Sarlikiotis, the excipients are non-toxic and provide satisfactory results to the pharmaceutical formulation.

Therefore, it would have been obvious to one of ordinary skill in the art at the time the invention was made to incorporate the excipients of Sarlikiotis within the formulation of Naclerio, because Sarlikiotis *et al.* explicitly teach a pharmaceutical formulation that comprises suitable excipients (i.e., glucose, lactose, maltose), whereby the excipients are non-toxic and aid in providing a satisfactory pharmaceutical formulation. The expected result would be an improved pharmaceutical formulation for treating respiratory disorders, as similarly desired by the Applicant.

Claims 61-65 are rejected under 35 U.S.C. 103(a) as being unpatentable over Sarlikiotis *et al.* (US Pat. No. 6,284,287) in view of Garvey *et al.* (US Pat. No. 5,824,669) as

applied to claims 1-9, 17-19, 24, 25, 54-56 and 59-60 above and further in view of Banholzer *et al.* (US Pat. No. 6,299,861 B1).

The instant invention is drawn to an inhalable powder pharmaceutical composition comprising: (a) a tiotropium salt; (b) an antihistamine; and (c) a pharmaceutically acceptable excipient selected from glucose, arabinose, lactose, saccharose or maltose, the tiotropium salt and the antihistamine optionally in the form of their enantiomers, mixtures of their enantiomers, their racemates, their solvates or their hydrates. The instant invention is also drawn to an inhalable powder pharmaceutical composition wherein the antihistamine comprises epinastine.

The teachings of Sarlikiotis *et al.* and Garvey *et al.* are delineated above. They do not teach epinastine.

Banholzer *et al.* ('861) teach ipratropium bromide active substance formulations administered by inhalation for respiratory tract therapy comprising in combination, an inhalable anti-allergic agent, such as epinastine (see reference column 3, lines 25-26); (Claim 7 and Abstract).

It would have been obvious to one of ordinary skill in the art at the time the invention was made to incorporate epinastine as taught by Banholzer *et al.* within the formulations of Sarlikiotis *et al.* or Garvey *et al.* because Banholzer *et al.* teach that anti-allergic agents (*i.e.*, epinastine) may be used as additional ingredients in combination with anticholinergic agents to provide for an enhanced and effective outcome. The expected result would be an improved pharmaceutical formulation with added benefits useful for respiratory tract therapies.

With regards to the instantly claimed ratios, the Examiner points out that, generally, differences in concentration will not support the patentability of subject matter encompassed by the prior art unless there is evidence indicating such concentration is critical. "[W]here the general conditions of a claim are disclosed in the prior art, it is not inventive to discover the optimum or workable ranges by routine experimentation". *In re Aller*, 220 F.2d 454, 456, 105 USPQ 233, 235 (CCPA 1955). In the instant case, Applicants have not demonstrated any surprising and/or unexpected results, attributable to the claimed ratios. The prior art clearly teaches similar inhalable pharmaceutical formulations, comprising mixtures of active compounds that contain anticholinergic agents in combination with antihistamines, whereby the compositions also contain suitable excipients (i.e., glucose, lactose, maltose) such as those instantly recited for the treatment of respiratory disorders. The prior art teaches similar components, used for the same field of endeavor and to treat the same problems as that desired by Applicant. Suitable or effective ratios can be determined by one of ordinary skill in the art through routine or manipulative experimentation to obtain the best possible results, as these are indeed variable parameters attainable within the art.

With regards to the instantly claimed tiotropium salt forms, (*i.e.*, hydrate, monohydrate), the prior art clearly teaches that the active compounds can be employed as free bases, acids or as pharmaceutically tolerable salts and counterions (see for instance, Sarlikiotis et al., col. 3, lines 55-65). Thus, this teaching sufficiently meets Applicant's claim limitation of a (mono)hydrate form. Moreover, Applicants have not demonstrated evidence of unexpected results, which accrue from the instantly claimed (mono)hydrate form.

Given the teachings of the prior art, the instant invention, when taken as a whole, would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made.

Correspondence

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Humera N. Sheikh whose telephone number is (571) 272-0604. The examiner can normally be reached on Monday through Friday from 8:00A.M. to 5:30P.M., alternate Fridays off.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Thurman Page, can be reached on (571) 272-0602. The fax phone number for the organization where this application or proceeding is assigned is (571) 273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have any questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

H. N. Sheikh H. N. Sheikh

Patent Examiner

Art Unit 1615

September 29, 2005